



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>4</sup> :</b>  <b>A61K 31/37</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 89/ 07939</b>  <b>(43) International Publication Date:</b> 8 September 1989 (08.09.89)
<b>(21) International Application Number:</b> PCT/US89/00450 <b>(22) International Filing Date:</b> 8 February 1989 (08.02.89) <b>(31) Priority Application Numbers:</b> 162,553 190,038 <b>(32) Priority Dates:</b> 1 March 1988 (01.03.88) 4 May 1988 (04.05.88) <b>(33) Priority Country:</b> US <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 190,038 (CIP) Filed on 4 May 1988 (04.05.88) <b>(71) Applicant (for all designated States except US):</b> THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).		<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> REUSSER, Fritz [US/US]; 6548 Trotwood Street, Portage, MI 49081 (US). TARPLEY, William, G. [US/US]; 5207 Mapler- idge, Kalamazoo, MI 49008 (US). DOLAK, Lester [US/US]; 3261 East B Avenue, Plainwell, MI 49080 (US). ALTHAUS, Irene, W. [US/US]; 10220 Shuman Street, Portage, MI 49002 (US).  <b>(74) Agent:</b> REYNOLDS, John, T.; Patent Law Depart- ment, The Upjohn Company, Kalamazoo, MI 49001 (US).  <b>(81) Designated States:</b> AT (European patent), AU, BE (Eu- ropean patent), CH (European patent), DE (Euro- pean patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US.  <b>Published</b> <i>Without international search report and to be repu-          blished upon receipt of that report.</i>
<b>(54) Title:</b> COUMARINS TO INHIBIT REVERSE TRANSCRIPTASE IN HUMANS		
<b>(57) Abstract</b>  The following compounds: 6-bromo-3-[(m-chlorophenyl)carbamoyl]-coumarin, 6-bromo-3-[( $\alpha,\alpha,\alpha$ -trifluoro-m-tolu- yl)carbamoyl]coumarin, 6-bromo-3-[(2,5-dichlorophenyl)carbamoyl]coumarin, [[bis(4-hydroxy-2-oxo-2H-1-benzopyran-3- yl)-methyl]cyclopentadienyl]cyclopentadienyl-iron, 3-cinnamoyl-4-hydroxy-coumarin, hexachlorocoumarin, 7-acetoxy- coumarin or [1-(2-oxo-2H-1-benzopyran-3-yl)ethylidene]-hydrazinecarboxylic acid phenylmethyl ester or pharmaceuti- cally acceptable salts thereof can be used to treat humans infected with one or more than one strain of a human immunodef- iciency virus.		

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COUMARINS TO INHIBIT REVERSE TRANSCRIPTASE IN HUMANSField of the Invention

This invention is a novel treatment of patients infected with a human immunodeficiency virus.

5 Background of the Invention

The compounds used to practice the method claimed in this invention are known; however, none of the compounds are known to be useful to treat humans infected with human immunodeficiency virus or strains thereof.

10 An estimated one to one and one-half million people in the United States are infected with a human retrovirus, the human immunodeficiency virus type I, HIV-1, which is the etiological agent of acquired immunodeficiency syndrome, "\$2-Billion Program Urged for AIDS", Norman, C., Science, Vol. 234, pages 661-662 (1986). Of those  
15 infected, an estimated two hundred and fifty thousands people will develop AIDS in the next five years, "The Epidemiology of AIDS: Current Status and Future Prospects", Curran, J.W., et al., Science, Vol. 229, No. 4720, pages 1352-1357 (1985). On March 20, 1987, the FDA approved the use of the compound, zidovudine (AZT), to treat AIDS  
20 patients with a recent initial episode of Pneumocystis carinii pneumonia, AIDS patients with conditions other than Pneumocystis carinii pneumonia or patients infected with the virus with an absolute CD4 lymphocyte count of less than  $200/\text{mm}^3$  in the peripheral blood. AZT is a known inhibitor of viral reverse transcriptase, an  
25 enzyme necessary for human immunodeficiency virus replication.

It is known in the art that certain antibiotics and polyanionic dyes inhibit retrovirus reverse transcriptase. None of the compounds claimed in this invention were known to specifically inhibit human immunodeficiency virus reverse transcriptase.

30 Summary of the Invention

This invention is a method for treating a human infected with one or more than one strain of a human immunodeficiency virus which comprises administering an effective amount of a compound selected from the group consisting of 6-bromo-3-[(m-chlorophenyl)carbamoyl]-  
35 coumarin, 6-bromo-3-[( $\alpha,\alpha,\alpha$ -trifluoro-m-toluy)carbamoyl]-coumarin, 6-bromo-3-[(2,5-dichlorophenyl)carbamoyl]-coumarin, [[bis(4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-methyl]cyclopentadienyl]cyclopentadienyl-iron, 3-cinnamoyl-4-hydroxy-coumarin, hexachlorocoumarin, 7-acetoxy-

coumarin or [1-(2-oxo-2H-1-benzopyran-3-yl)ethylidene]-hydrazinecarboxylic acid phenylmethyl ester or pharmaceutically acceptable salts thereof, to the infected human.

Detailed Description of the Invention

5        In this document, the term human immunodeficiency virus means human immunodeficiency virus type I, human immunodeficiency virus type II, or strains, apparent to one skilled in the art, which belong to the same viral family and which create similar physiological effects in humans as human immunodeficiency virus types I or II.

10        The structural formulas, if known, of each of the compounds used to practice the method claimed in this invention are given in the structure charts. The following compounds; 6-bromo-3-[(m-chloro-phenyl)carbamoyl]-coumarin, 6-bromo-3-[( $\alpha,\alpha,\alpha$ -trifluoro-m-toluy)]-carbamoyl]-coumarin, and 6-bromo-3-[(2,5-dichlorophenyl)carbamoyl]-  
15        coumarin, were obtained commercially. The preparation of the compound, 3-cinnamoyl-4-hydroxy-coumarin, is described in "Zur Chemie des 4-Hydroxy-cumarins", Monatshefte fur chemi, Vol. 87, pages 439-446 (1956). The preparation of the compound, 7-acetoxycoumarin, is described in Chem. Ber., Vol. 12, pages 993-999 (1879). The com-  
20        pound, hexachlorocoumarin, is prepared when chlorine is bubbled into an ethanolic solution of coumarin in the presence of light. When there is no longer any detectable presence of the starting material in solution, the solvent is removed and the mixture of polychlorinated products is separated by chromatography. The compound, [[bis-  
25        (4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-methyl]cyclopentadienyl]cyclopentadienyl-iron, is prepared by condensing 2.0 equivalents of commercially available 4-hydroxycoumarin with 1.5 equivalents of commercially available ferrocenecarboxaldehyde in ethanol following the general procedures described by Sullivan, et al., JACS, Vol. 65, July-December, pages 2288-2291 (1943) "Studies on 4-Hydroxycoumarins.  
30        II. The Condensation of Aldehydes with Hydroxycoumarins". The compound, [1-(2-oxo-2H-1-benzopyran-3-yl)ethylidene]-hydrazinecarboxylic acid phenylmethyl ester, is prepared by condensing commercially available 3-acetylcoumarin with commercially available benzyl carbamate in the presence of glacial acetic acid in absolute methanol. The  
35        reagents are refluxed, diluted with water, cooled and filtered to provide the crystalline compound.

These compounds or pharmaceutically acceptable salts thereof can

be used and administered in practicing the method claimed in this invention. Pharmaceutically acceptable salts refers to those salts of the compounds claimed in this invention which would be readily apparent to a manufacturing pharmaceutical chemist to be equivalent to the parent compound in properties such as formulation, stability, patient acceptance and bioavailability.

Those skilled in the art would know how to formulate the compounds used to practice the method claimed in this invention into appropriate pharmaceutical dosage forms. Examples of the dosage forms include oral formulations, such as tablets or capsules, or parenteral formulations, such as sterile solutions.

When the compounds used to practice the method claimed in this invention are administered orally, an effective amount is from about 1 to 100 mg per kg per day. A typical unit dose for a 70 kg human would be from about 200 mg to 1000 mg taken one to four times per day. Either solid or fluid dosage forms can be prepared for oral administration. Solid compositions are prepared by mixing the compounds used to practice the method claimed in this invention with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methyl cellulose, or functionally similar pharmaceutical diluents and carriers. Capsules are prepared by mixing the compounds used to practice the method claimed in this invention with an inert pharmaceutical diluent and placing the mixture into an appropriately sized hard gelatin capsule. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compounds used to practice the method claimed in this invention with an acceptable inert oil such as vegetable oil or light liquid petrolatum. Syrups are prepared by dissolving the compounds used to practice the method claimed in this invention in an aqueous vehicle and adding sugar, aromatic flavoring agents and preservatives. Elixirs are prepared using a hydroalcoholic vehicle such as ethanol, suitable sweeteners such as sugar or saccharin and an aromatic flavoring agent. Suspensions are prepared with an aqueous vehicle and a suspending agent such as acacia, tragacanth, or methyl cellulose.

When the compounds used to practice the method claimed in this invention are administered parenterally, it can be given by injection or by intravenous infusion. An effective amount is from about 1 to

100 mg per kg per day. Parenteral solutions are prepared by dissolving the compounds used to practice the method claimed in this invention in water and filter sterilizing the solution before placing in a suitable sealable vial or ampule. Parenteral suspensions are prepared in substantially the same way except a sterile suspension vehicle is used and the compounds used to practice the method claimed in this invention are sterilized with ethylene oxide or suitable gas before it is suspended in the vehicle.

The exact route of administration, dose, or frequency of administration would be readily determined by those skilled in the art and is dependant on the age, weight, general physical condition, or other clinical symptoms specific to the patient to be treated.

Patients to be treated would be those individuals: 1) infected with one or more than one strain of a human immunodeficiency virus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) having either a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isoporiasis, iii) bronchial and pulmonary candidiasis including pneumocystis pneumonia iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4 lymphocyte count of less than  $200/\text{mm}^3$  in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the compounds disclosed herein in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

Without further elaboration, those skilled in the art can practice the present invention to its fullest extent. The following detailed examples further describe how to use the compounds claimed in this invention to treat humans infected with one or more than one strain of a human immunodeficiency virus. These examples are merely illustrative and are not limitations of the preceding disclosure. Those skilled in the art will promptly recognize appropriate variations from the examples. In each example, any compound claimed in this invention could replace the compound used in the particular example.

#### Example 1      Hard Gelatin Capsules

One thousand two-piece hard gelatin capsules for oral use, each capsule containing 50 mg of hexachlorocoumarin, are prepared from the

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following:

	Hexachlorocoumarin	50 gm
	Lactose	100 gm
	Cornstarch	20 gm
5	Talc	20 gm
	Magnesium Stearate	2 gm

The hexachlorocoumarin is added to the other ingredients, mixed and encapsulated in the usual manner.

Example 2          Tablets

10          One thousand tablets, each containing 50 mg of hexachlorocoumarin, are prepared from the following:

	Hexachlorocoumarin	50 gm
	Lactose	75 gm
	Cornstarch	50 gm
15	Magnesium Stearate	4 gm
	Light liquid petrolatum	5 gm

20          The hexachlorocoumarin is added to the other ingredients, mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets.

Example 3          Parenteral solution

A sterile aqueous solution for parenteral intravenous injection containing 150 mg of hexachlorocoumarin in one liter of solution is prepared from the following:

25	Hexachlorocoumarin	150 mg
	Water for injection, qs	1000 mg

The hexachlorocoumarin is sterilized, added to the sterile water, filled into sterile containers and sealed.

30          The utility of this invention is demonstrated by the ability of the compounds used to practice the method claimed in this invention to inhibit viral reverse transcriptase, an enzyme essential for human immunodeficiency virus replication. This enzyme has characteristics which differentiate it from other known cellular polymerases and it is a unique enzyme which is not found in uninfected cells. Viral  
35          reverse transcriptase is found in extracts from bacterial clones prepared according to the procedure described by Goff, S. P., et al., Journal of Virology, Vol. 59, No. 3, pages 743-745 (1986) "Expression of Reverse Transcriptase Activity of Human T-lymphotropic Virus Type

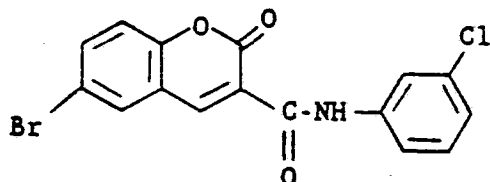
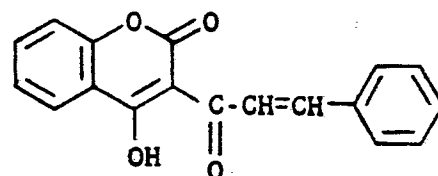
III (HTLV-III/LAV) in *Escherichia coli*". Inhibition of this enzyme is determined in a cell free assay which measures the level of radioactive precursors incorporated into DNA. Extracts prepared according to the procedure of Kleid, D. G., et al., Science, Vol. 214, No. 4525, pages 1125-1129 (1981) "Cloned Virla Protein Vaccine for Foot-and-Mouth Disease: Responses in Cattle and Swine" are incubated in a mixture of inhibitor, 20 mM dithiothreitol, 60 mM sodium chloride, 0.05% NP-40, 10 mM magnesium chloride, 50 mM Tris pH 8.3, 10  $\mu$ M [<sup>35</sup>S]-labeled deoxynucleoside-5'-triphosphate, 10  $\mu$ g/ml RNA template (poly rC or poly rA) and 5  $\mu$ g/ml DNA primer (oligo dG or oligo dT) for 30 minutes at 37°C. Incorporation of radio-labeled precursor is determined by spotting aliquots of the reaction mixture on DE81 paper, washing the papers to remove unincorporated precursor, drying and determining counts. Table 1 contains the results of the assay for the compounds used to practice the method claimed in this invention.



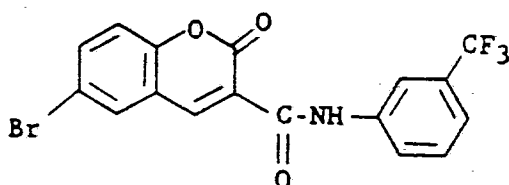
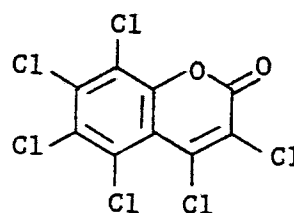
-7-

TABLE 1

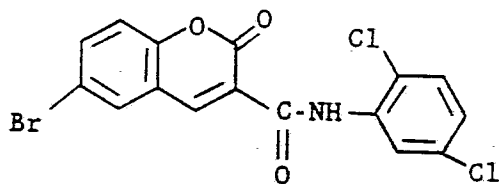
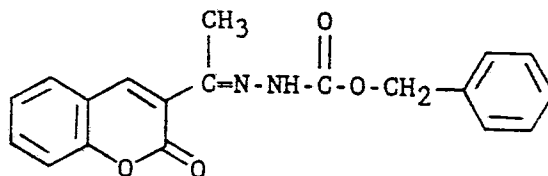
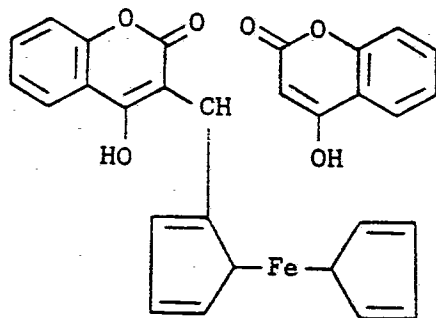
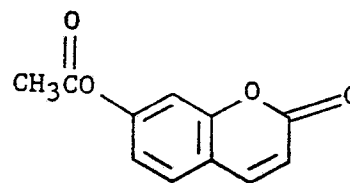
	<u>COMPOUND (0.1 mM)</u>	<u>%INHIBITION</u>
5	6-bromo-3-[(m-chlorophenyl)- carbamoyl]-coumarin	28
	6-bromo-3-[( $\alpha,\alpha,\alpha$ -trifluoro- m-toluy)carbamoyl]-coumarin	31
10	6-bromo-3-[(2,5-dichlorophenyl)- carbamoyl]-coumarin	42
15	[[bis(4-hydroxy-2-oxo-2H-1-benzo- pyran-3-yl)-methyl]cyclopentadienyl]- cyclopentadienyl-iron	60
	3-cinnamoyl-4-hydroxy-coumarin	35
20	hexachlorocoumarin	34
	[1-(2-oxo-2H-1-benzopyran-3-yl)- ethylidene]-hydrazinecarboxylic acid phenylmethyl ester	31
25	7-acetoxycoumarin	23

STRUCTURE CHART6-bromo-3-[(m-chlorophenyl)-  
carbamoyl]-coumarin

3-cinnamoyl-4-hydroxy-coumarin

6-bromo-3-[α,α,α-trifluoro-  
m-toluy]carbamoyl]-coumarin

hexachlorocoumarin

6-bromo-3-[(2,5-dichlorophenyl)-  
carbamoyl]-coumarin[1-(2-oxo-2H-1-benzopyran-3-yl)-  
ethylidene]-hydrazinecarboxylic  
acid phenylmethyl ester[[bis(4-hydroxy-2-oxo-2H-1-benzo-  
pyran-3-yl)-methyl]cyclopentadi-  
enyl]cyclopentadienyl-iron

7-acetoxycoumarin

CLAIMS

1. Use of a compound selected from the group consisting of 6-bromo-3-[(m-chlorophenyl)carbamoyl]-coumarin, 6-bromo-3-[( $\alpha,\alpha,\alpha$ -trifluoro-m-toluy1)carbamoyl]-coumarin, 6-bromo-3-[(2,5-dichlorophenyl)carbamoyl]-coumarin, 5 [[bis(4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-methyl]-cyclopentadienyl]cyclopentadienyl-iron, 3-cinnamoyl-4-hydroxy-coumarin, hexachlorocoumarin, 7-acetoxycoumarin or [1-(2-oxo-2H-1-benzopyran-3-yl)ethylidene]-hydrazinecarboxylic acid phenylmethyl ester or 10 a pharmaceutically acceptable salt thereof, to prepare a medicament to treat a human infected with one or more strains of a human immunodeficiency virus.
2. A method according to claim 1 where the effective amount of the 15 compound is from about 1 to 100 mg per kg per day.
3. A method according to claim 1 where the compound is 6-bromo-3-[(m-chlorophenyl)carbamoyl]-coumarin.
- 20 4. A method according to claim 1 where the compound is 6-bromo-3-[( $\alpha,\alpha,\alpha$ -trifluoro-m-toluy1)carbamoyl]-coumarin.
5. A method according to claim 1 where the compound is 6-bromo-3-[(2,5-dichlorophenyl)carbamoyl]-coumarin.
- 25 6. A method according to claim 1 where the compound is [[bis(4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-methyl]cyclopentadienyl]cyclopentadienyl-iron.
- 30 7. A method according to claim 1 where the compound is 3-cinnamoyl-4-hydroxy-coumarin.
8. A method according to claim 1 where the compound is hexachlorocoumarin.
- 35 9. A method according to claim 1 where the compound is 7-acetoxycoumarin.

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10. A method according to claim 1 where the compound is [1-(2-oxo-2H-1-benzopyran-3-yl)ethylidene]-hydrazinecarboxylic acid phenyl-methyl ester.



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**(54) Title:** COUMARINS TO INHIBIT REVERSE TRANSCRIPTASE IN HUMANS

**(57) Abstract**

The following compounds: 6-bromo-3-[(m-chlorophenyl)carbamoyl]-coumarin, 6-bromo-3-[( $\alpha,\alpha,\alpha$ -trifluoro-m-tol-yl)carbamoyl]coumarin, 6-bromo-3-[(2,5-dichlorophenyl)carbamoyl]coumarin, [[bis(4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-methyl]cyclopentadienyl]cyclopentadienyl-iron, 3-cinnamoyl-4-hydroxy-coumarin, hexachlorocoumarin, 7-acetoxy-coumarin or [1-(2-oxo-2H-1-benzopyran-3-yl)ethylidene]-hydrazinecarboxylic acid phenylmethyl ester or pharmaceutically acceptable salts thereof can be used to treat humans infected with one or more than one strain of a human immunodeficiency virus.

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of Korea  
KR Republic of Korea  
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SN Senegal  
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TD Chad  
TG Togo  
US United States of America

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 89/00450

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>4</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>4</sup> : A 61 K 31/37																	
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px;">IPC<sup>4</sup></td> <td style="padding: 5px;">A 61 K 31/00</td> </tr> </table> <div style="text-align: center; margin-top: 10px; font-size: small;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup></div>			Classification System	Classification Symbols	IPC <sup>4</sup>	A 61 K 31/00											
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IPC <sup>4</sup>	A 61 K 31/00																
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; text-align: left; padding: 5px;">Category <sup>*</sup></th> <th style="width: 70%; text-align: left; padding: 5px;">Citation of Document, <sup>11</sup> with Indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 20%; text-align: left; padding: 5px;">Relevant to Claim No. <sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">Rev. Bras. de Pesquisas Méd. e Biol., vol. 8, nos. 5-6, 1975, F.W. Eichbaum: "Anticoagulents and cancer. A review", pages 489-496, see page 491, column 2, lines 26-30 --</td> <td style="vertical-align: top; padding: 5px;">1,7</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">P,A</td> <td style="padding: 5px;">Proceedings of AACR, vol. 29, March 1988, B. Omarbasha et al.: "Decrease prostatic size in response to Coumarin treatment", page 372, abstract 1479, see the abstract --</td> <td style="vertical-align: top; padding: 5px;">1,7</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">P,A</td> <td style="padding: 5px;">Chemical and Pharmaceutical Bulletin, vol. 36, no. 6, June 1988 (Tokyo, JP), Tsutomu Hatano et al.: "Anti-human immunodeficiency virus phenolics from licorice", pages 2286-2288, see the abstract; page 2287, formulas --</td> <td style="vertical-align: top; padding: 5px;">1,7</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">Microbiologica, vol. 8, 1985, O.E. Varnier et al.: "Antiviral ./.</td> <td style="vertical-align: top; padding: 5px;">1,7</td> </tr> </tbody> </table>			Category <sup>*</sup>	Citation of Document, <sup>11</sup> with Indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	A	Rev. Bras. de Pesquisas Méd. e Biol., vol. 8, nos. 5-6, 1975, F.W. Eichbaum: "Anticoagulents and cancer. A review", pages 489-496, see page 491, column 2, lines 26-30 --	1,7	P,A	Proceedings of AACR, vol. 29, March 1988, B. Omarbasha et al.: "Decrease prostatic size in response to Coumarin treatment", page 372, abstract 1479, see the abstract --	1,7	P,A	Chemical and Pharmaceutical Bulletin, vol. 36, no. 6, June 1988 (Tokyo, JP), Tsutomu Hatano et al.: "Anti-human immunodeficiency virus phenolics from licorice", pages 2286-2288, see the abstract; page 2287, formulas --	1,7	A	Microbiologica, vol. 8, 1985, O.E. Varnier et al.: "Antiviral ./.	1,7
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<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p><sup>*</sup> Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>																	
<b>IV. CERTIFICATION</b> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">           Date of the Actual Completion of the International Search            1st June 1989         </td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">           Date of Mailing of this International Search Report            28. 09. 89         </td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;">           International Searching Authority            EUROPEAN PATENT OFFICE         </td> <td style="border-bottom: 1px solid black; padding: 5px;">           Signature of Authorized Officer  <div style="text-align: right; font-size: large; font-weight: bold;">T.K. WILLIS</div> </td> </tr> </table>			Date of the Actual Completion of the International Search 1st June 1989	Date of Mailing of this International Search Report 28. 09. 89	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer <div style="text-align: right; font-size: large; font-weight: bold;">T.K. WILLIS</div>											
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## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

activity of coumermycin identification  
of resistant and sensitive retrovirus  
strains", pages 283-287, see the  
abstract; page 286, lines 12-17

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V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 2..... because they relate to subject matter not required to be searched by this Authority, namely:  
See PCT-Rule 39.1(IV); methods for treatment of the human  
or animal body by surgery or therapy,  
as well as diagnostic methods.
2. ☐ Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:  
1,7
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.